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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/066,320

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Jonathan S. Stamler

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12/11/2007

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EXAMINER

GUPTA, ANISH

ART UNIT

PAPER NUMBER

1654

MAIL DATE

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12/11/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/066,320	<b>Applicant(s)</b> STAMLER ET AL.	
	<b>Examiner</b> Anish Gupta	<b>Art Unit</b> 1654	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 9-19-07.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 36,37,40,41 and 44-47 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 36,37,40,41 and 44-47 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |                                                                                                            |                                                                                         |
|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                                           | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____                                                |

## DETAILED ACTION

### DETAILED ACTION

1. The amendment filed, 9-19-07, is acknowledged. Claims 31-35, 38, 39, 42, 43 were canceled. Claims 36, 40, were amended. Claims 44-47 have been added.

2. All rejections made in the previous office action are hereby withdrawn. Note that a New Matter rejection follows below. If Applicants amend the claims by deleting the new matter, thereby reverting back to the claims filed 1-18-07, the previous rejection will again be reinstated.

### New Grounds For Rejections

#### *Claim Rejections - 35 USC § 112*

#### New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 36-37, 40, 41, 44-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims have been amended to recite "(c) preserving redox chemistry of hemoglobin by adding a redox modifier wherein the redox modifier is a nitrite."

The amendment to the claims of adding redox modifier as a nitrite is deemed to be new matter.

#### Lack of Ipsis Verbis Support

The instant application, defines "Redox chemistry" refers to the transfer of NO from the heme Fe to cysteine on the .beta. subunit with the loss of an electron. See, for example, WO 98/34955 regarding the conversion of iron nitrosyl-hemoglobin to SNO-hemoglobin." See page 22. The specification does not recite any the use of nitrites, nor any other specific agent for that matter, should be utilized to preserve redox chemistry. While the specification recites nitrite as redox modifiers, the specification does not specifically state that these redox modifiers are used to preserve redox chemistry.

#### Lack of Inherent Support

"While there is no in haec verba requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." See MPEP 2163. In their response, Applicants referenced page 22-23 for support for the addition of nitrite to preserve redox chemistry. In reviewing page 22-23, it is unclear where such support can be found. The only reference made regarding nitrite is in the paragraph bridging page 22-23, which states "[i]n addition, it is demonstrated that cooperativity of NO binding is not sufficient for transformation of NO into bioactive form (see FIG. 3C and FIG. 3D, borate). Thus, by regulating the auto-oxidation function of hemoglobin in vacancies (e.g., 10 millimolar phosphate vs. borate) or by adding redox modifiers such as nitrite, one can greatly enhance the transformation into SNO or DNIC." The sentence regarding the addition of redox modifiers to enhance the transformation of SNO or DNIC does not imply that preservation of redox chemistry is achieved. The only conclusion one can make

from this sentence is that nitrites, much like 10 mm phosphate, enhance SNO or DNIC. One cannot make any conclusion that the nitrites are responsible for "transfer of NO from the heme Fe to cysteine on the .beta. subunit with the loss of an electron." In fact, the specification does not make reference at any point that the nitrites are used to preserve redox chemistry. Thus, one cannot readily conclude that the specification contains inherent or implicit support for the amended claims.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 36-37, 40, 41, 44-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

*(1) The nature of the invention:*

The invention is drawn to Nitric Oxide and its interaction with various forms of hemoglobin.

*(2) The state of the prior art*

The prior art states nitric oxide, when introduced with oxyhemoglobin, results in the formation of methemoglobin. "Methemoglobin formation occurred instantaneously on addition of NO." (see page 222 of Jia). Yonetani et al. States Free NO in the plasma constantly diffuses into the erythrocyte and immediately reacts with Hb, which acts as a NO scavenger. It has been generally assumed that free NO in the blood is scavenged by rapid reaction with oxyHb to produce such bio-inactive products as metHb and nitrate under physiological conditions (see paragraph bridging col. 1-2). Nitric oxide in the blood rapidly diffuses into erythrocytes and reacts with oxyHb to form metHb and  $\text{NO}_2^-$  /  $\text{NO}_3^-$  (see col. 16, lines 5-10). Stamler et al. (US6884773) teaches when  $\text{Hb(FeII)O}_2$  is incubated with excess nitric oxide or nitrite, methemoglobin ( $\text{HbFe[III]}$ ) forms rapidly (see col. 9, lines 16-25). The reference further states that conversion of oxyHb ( $\text{Hb[FeII]O}_2$ ) to metHb ( $\text{HbFe[III]}$ ) is observed upon incubation of oxyHb with increasing concentrations of NO. In reaction mixtures containing NO and oxyHb in ratios of 1:1, 2:1 and 10:1, respectively, Methemoglobin formation occurred instantaneously on addition of NO (i.e. within instrument dead time) (See example 1 in col 23).

*(3) The relative skill of those in the art*

The relative skill of the those in the art is high.

*(4) The predictability or unpredictability of the art*

Given the state of the art, it is relatively predictable to conclude that when nitric oxide or nitrite with combined with oxyhemoglobin will result in the formation of methemoglobin.

*(5) The breadth of the claims*

Claim 36 has been amended to recite "A method for producing S-nitrosohemoglobin, said method comprising the addition of free NO to oxyhemoglobin under conditions to produce S-nitrosohemoglobin, said conditions comprising:

- (a) adding free NO in an amount sufficient to produce S-nitrosohemoglobin;
- (b) maintaining the R structure of hemoglobin; and,
- (c) preserving the redox chemistry of hemoglobin[[,]] by adding a redox modifier, wherein the redox modifier is nitrite;

wherein the conditions for maintaining the R structure of hemoglobin comprise a phosphate concentration that is less than 100 mM and wherein the conditions for preserving the redox chemistry of hemoglobin occur in the absence of borate."

*(6) The amount of direction or guidance presented and (7) The presence or absence of working examples*

The specification is silent as to the conditions necessary to achieve the claimed product of S-nitrosylHb. It is not always the case that when NO and nitrite is added to oxyhemoglobin that S-nitrosylHb is obtained. For example, Example 3 of the specification shows the effects of free NO to oxyhemoglobin. The prior art also reflects the concept that NO added to oxyhemoglobin does not always lead to the formation of S-nitrohemoglobin. Jia, as Applicant asserted on page 4 of the

response dated 2-25-05, reports that addition of free NO to oxyhemoglobin produces methemoglobin rather than S-nitrosohemoglobin (see page 222, figure 1B). Yonetani et al. teaches that Nitric oxide in the blood is well maintained at a steady-state level of the order of micromolar by the dynamic balance between the continuous supply of NO by endothelial NO syntheses and other sources and the rapid scavenging of NO by oxy hemoglobin (oxyHb) in the erythrocytes. Nitric oxide in the blood rapidly diffuses into erythrocytes and reacts with oxyHb and forms metHb and NO.sub.2.sup.- /NO.sub.3.sup.- (see col. 16, lines 1-8).). Stamler et al. (US6884773) teaches when Hb(FeII)O.sub.2 is incubated with excess **nitric oxide or nitrite**, methemoglobin (HbFe[III]) forms rapidly (see col. 9, lines 16-25). The reference further states that conversion of oxyHb (Hb[Fe[II]O.sub.2) to metHb (HbFe[III]) is observed upon incubation of oxyHb with increasing concentrations of NO. In reaction mixtures containing NO and oxyHb in ratios of 1:1, 2:1 and 10:1, respectively, Methemoglobin formation occurred instantaneously on addition of NO (i.e. within instrument dead time) (See example 1 in col 23).

Here, the claimed invention requires the addition of both nitric oxide and nitrite to oxyhemoglobin to produce S-nitrosohemoglobin. The claims are silent with respect to the amount of nitrite necessary to preserve redox chemistry. Similarly the specification is silent with respect the amount of nitrite present to preserve redox chemistry. Such information is necessary because the presence of nitric oxide and nitrite result in the formation of methemoglobin and not S-nitrosohemoglobin. Given these teachings, one cannot readily conclude that addition of free NO and nitrite to oxyhemoglobin or oxygenated erythrocytes will result in the formation of S-nitrosohemoglobin, as the claims currently recite. Rather specific conditions are necessary to make desired end product.

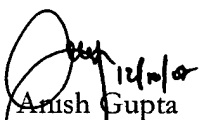
*(8) the quantity of experimentation necessary*

For the reasons set forth above, one would be burdened with undue experimentation in determining the appropriate conditions for obtaining S-nitrosylhemoglobin rather than obtaining methemoglobin or iron-nitrosylhemoglobin.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (571)272-0965. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can normally be reached on (571) 272-0562. The fax phone number of this group is (571)-273-8300.

  
Anish Gupta  
Patent Examiner